Prognostic factors in stage III-IV adrenocortical carcinomas (ACC): an European Network for the Study of Adrenal Tumor (ENSAT) study.

PROGNOSTIC FACTORS IN STAGE III-IV ADRENOCORTICAL CARCINOMAS (ACC): AN EUROPEAN NETWORK FOR THE STUDY OF ADRENAL TUMOR (ENSAT) STUDY.

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Prognostic factors of synchronous Stage III and IV adrenocortical carcinomas (ACC): an ENS@T study.

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For the number of the authors: we divided the n of pts in the cohort by the n of habitants in each country:

-Germany: 237/82 millions: 2.9/millions/habitants

-France: 153/65 M : 2.4/millions

-Italy : 60/61 M : 1/M hab

-Netherlands : 13/16.7 M : 0.75/hab

Then we multiply for 3:

-Germany: 3*3→9

-France : 2.5*3→7.5→ 8

-Italy : 1*3→ 3

-Netherlands : 0.75*3 →2.25→3 (1 to add)

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Background The clinical course of advanced adrenocortical carcinoma (ACC) is heterogeneous. The primary objective of our study was to refine and progress in the prognostic stratification of advanced ACC.

Methods Patients with advanced ENS@T stage III or with synchronous stage IV ACC registered between 2000 and 2009 in the ENS@T databasis were enrolled. Primary endpoint

was overall survival (OS). Parameters with potential prognostic relevance were captured. Univariate and multivariate analyses were performed: model 1 “prior surgery”; model 2 "post surgery".

Results Four hundred and forty-four patients with advanced ENS@T (stage III: 210; stage IV 234 patients) were analysed. After a median follow-up of 55.2 months, median overall survival was 24 months. A modified ENS@T (mENS@T) classification was validated as defined by: stage III in case of invasion in surrounding tissues/organs or vena renalis/cava or, stage IVa, IVb, IVc in case of 2, 3 or >3 metastatic organs including the N, respectively. Five yr OS was 49%, 15%, 11% and 0% for mENSAT stages III, IVa, IVb and IVc , respectively ($p<0.0001$). At multivariate analysis, mENS@T stage (HR:2.6, HR:3.8 or HR:4.9 for stage IVa, IVb, or IVc respectively, all $p<0.0001$) and 4 additional parameters were significantly associated to OS: age$\geq$50 years (HR:1.6, $p<0.0001$), presence of tumor or hormonal-related symptoms (HR:1.6, $p=0.01$;(HR:1.6, $p=0.03$) in model 1 but also R status (for R1/2/x HR:1.7, $p=0.0006$), grade (Weiss >6 and Ki67>20%, HR:1.3, $p=0.06$) in model 2.

Conclusion: mENS@T classifications and GRAF parameters (Grading, R status, Age, and Functional symptoms) were found to best stratify the prognosis of advanced ACC patients.

Introduction

Adrenocortical carcinoma (ACC) is a rare malignancy with an estimated incidence of 0.7–2.0 cases per million habitant per year (1, 2). ACC is considered one of the most aggressive solid tumor in oncology as testified by a 5-year survival below 15% for metastatic patients in four registries (3-6). Historically, ACC prognosis has been shown to be mainly driven by the presence of metastases and tumor resectability (7,8). More recently, the European Network for the Study of adrenal Tumors (ENS@T) classification of TNM stage and the resection status have refined prognostication (5, 6, 9, 10).

Advanced ACC, defined as tumor stage III, in case of loco-regional spread, or stage IV, in case of distant metastases, represent 18-26% and 21-46% of ACC patients at diagnosis, respectively (3-6). Treatment options of these patients are limited (11-13) and no predictors of response is validated. The best way to stratify stage III and/or IV ACC patients prognosis is a matter of debate. Indeed, several studies have suggested that stage III patients with positive lymph nodes or vena cava invasion could have a similar prognosis than stage IV patients (9, 14, 15). In stage IV ACC patients, the number of tumor affected organs has been reported to be of value in refining the prognosis of these patients as well (16). In addition, several studies suggested that age, secretion of hormones, Weiss score and/or proliferative index and the resection (R) status may also affect the prognosis of these patients (10, 17-20). An improved prognostic stratification is therefore needed to better understand the heterogeneity of prognosis in advanced ACC as illustrated by the 2 to 190 months range overall survival reported in studies investigating treatment with mitotane (21-26).

The objective of this retrospective study was to refine the prognostic classification of advanced stage III and synchronous stage IV ACC patients. To achieve this goal, the ENS@T registry, encompassing a large number of ACC treated in expert centers from four European countries, was utilized.

Patients and Methods

Patients and data collection

From January 1, 2000 to December 31, 2009, 463 patients with stage III or IV ACC followed in 16 expert referral centers of four European countries (Germany, France, Italy and Netherlands) were consecutively registered in a central computerized database: the

European network for the Study of Adrenal tumors (ENS@T) ACC Registry. Inclusion criteria were: confirmed histological diagnosis of ACC, stage III-IV at imaging and/or surgery performed within 3 months of primary diagnosis, age above 18 years and availability of follow-up data.

Data collected included the following items at the time of diagnosis: age, gender, modality of tumor diagnosis (as defined by: incidental, symptom- or, hormone-related to tumor mass or other/unknown), items of ENS@T or UICC TNM classifications (tumor size, invasion in adjacent tissue/organs or vena cava/renal vein, lymph node or distant metastases), tumor grading based on the pathological primary tumor analysis (defined by the median Weiss score (≤6/>6) or median Ki67 percentage (<20%/≥20%), R status at first surgery including the primary and metastasis (complete resection: R0; microscopic residual resection: R1; macroscopic residual disease: R2, resection not known: Rx).

All parameters were captured based on per-investigator file and collected through a dedicated e-CRF.

Both registries had been approved by the local ethics committees of all partaking centers and all included patients had provided written informed consent.

Evaluation of different stage III-IV definitions and tumoral grading systems

Since recent publications have suggested that tumors with N1 status or venous invasion could behave like stage IV metastatic disease, but also that the number of metastatic organs in stage IV ACC patients could help refining the classification (14-16), we first attempted to validate the best way to stratify the TNM of advanced stage III-IV ACC patients. Four different TNM classification systems were analyzed prior the final prognostic analysis: UICC, ENS@T classifications (6), but also two proposed modified ENS@T classifications (mENS@T) that classify either N1-Nx patients or venous invasion as stage IV and categorize stage IV according to the number of tumor organs (Figure 1). Selection and combination of parameters was performed graphically, using Kaplan-Meier and the Hall-Wellner confidence interval of each curve. The parameters that were selected to best reflect tumor burden were those allowing the greatest discrimination of patients in terms of OS, graphically.

Based on previous reports that suggest a prognostic role for the Weiss score and or proliferative index in advanced ACC patients (18, 27), we also first attempted to validate the best way to classify the pathological parameters as a Grading system for advanced stage III-IV ACC patients according to the median Weiss score and or Ki67 index based on the

primary tumor analysis (Figure 2). Like for tumor burden, selection of parameters to express tumoral grade was performed graphically using Kaplan-Meier curves.

Statistical analysis

Descriptive analyses were performed using mean and standard-deviation for quantitative variables, and comparisons were performed using Student test (or non-parametric Wilcoxon test if non-normally distributed). Qualitative variables were expressed in percentage and comparisons were performed using chi-square test.

The primary endpoint was overall survival (OS), defined as the interval between date of stage III and IV ACC diagnosis and death of any cause. Surviving patients were censored at the date of last follow-up. Follow-up data were last updated for November 2012. The median follow-up was estimated by the reverse Kaplan-Meier method (Schemper's method).

Survival rates and 95% confidence interval were estimated by the Kaplan-Meier method. The log-rank test was used to compare survival curves. Parameters significantly associated with OS in univariate analysis ($p<0.05$) were further tested in the multivariate analysis. Hazard-ratio (HR) and 95% confidence interval (95%CI) were estimated using Cox's proportional hazards regression model at multivariate analysis, with the lowest risk group as the reference group. All tests were two-sided.

The following variables were analysed for their potential prognostic value at univariate analysis: age (<50 or $\geq$50 years), gender, modality of diagnosis (tumor mass, incidental mass, hormonal hypersecretion), tumor size (0-50 mm, 50-100 mm, 100-200 mm and >200mm), best staging system as defined above, type of organ involved (lung, liver, bone, distant lymph nodes), R status and pathological grading as defined above.

Two multivariate analyses were performed: ***model 1*** called "prior-surgery" analysed all prognostic parameters available at the time of ACC diagnosis. ***Model 2*** called "post-surgery" analysed all prognostic parameters including the grading and R status. Statistical analysis was conducted using SAS software version 9.2.

Results

Population characteristics and follow-up data

The following exclusion criteria were applied to the 463 cases reviewed: age younger than 18 years old (15 patients), loss to follow-up (4 patients). Therefore, 444 patients constitute the studied population: 210 (47%) were classified ENS@T stage III and 234 (53%) were stage IV. The main clinical features are summarized in Table 2. Briefly, the majority of patients were females (61%) with a median age of 51±14 years. Symptoms related to tumor mass were present in 163 (37%), hormonal hypersecretions were present in 144 (32%) patients including cortisol hypersecretion in 116 (80%) patients.

Based on TNM staging, 11 (2%) were staged as T1, 97 (22 %) as T2, 140 (32%) as T3, and 196 (44%) as T4, respectively. Positive regional lymph nodes (N1) as defined by both imaging and pathology were found in 98 (22%) cases. Lung, liver, or bone metastases were found in 152 (34%), 125 (28%) and 32 (7%) of cases, respectively. In stage IV patients, the number of involved organs including the primary and the N status was 2 in 119 (27%), and at least 3 in 111 (26%) patients. R status was recorded in 279 (62%) of patients and an R0 status was achieved in 152 cases of them (54%) including the surgery of the primary or the primary and additional organs in 109 or 43 patients, respectively. Fifty-four patients (all stage IV) do not underwent surgery.

Weiss score was captured in 327 cases (73%) and was found above 6 in 153 (47%) tumors. Ki67 index was captured in 226 patients (50%) and found above 20% in 123 (54%) of cases.

The median follow-up of patients was 55.2 months. Median overall survival was 24 months. The 1-, 2- and 5-yr survival rates were 71%, 50% and 27%, respectively. Three hundred and one patients (68%) died during the time of the study. Among the 143 patients still alive at the time of data freeze: 76 (53%) were alive with metastatic or recurrence disease and 63 (44%) without evidence of disease, status was unknown in 4 patients. Death was ACC-related in all cases except in six.

Evaluation of the best TNM and pathological classifications in advanced ACC patients

Both ENS@T and the mENS@T classification, as defined in Materials and Methods, were found more informative than UICC (Figure 1). Finally, because the first mENS@T classification was found to better stratify the prognosis of stage III-IV ACC patients we finally

used the following mENS@T classification as defined by: stage III (T3-4N0M0) or, stage IVa, IVb, IVc according to the number of tumor organs involved including the primary tumor and lymph node status as “organ”: 2, 3 or >3, respectively (Supplementary Figure 1 a-b, Table 1). Regarding the grading, prognostic information but also the number of data available was taken into account. Both Ki67 and the Weiss score significantly discriminate OS outcome at univariate analysis. However, Ki67 capture was lacking in a significant number of patients. Weiss score and/or Ki67 were available in 350 patients and the combination of the two pathological parameters (Weiss ≤ 6 and Ki67<20 vs Weiss >6 or Ki67≥20) allowed to significantly separate two subgroups of patients, in terms of OS (Figure 2a-c). We finally classified the grading of advanced ACC patients according to the following classification as defined by: Weiss score > 6 or Ki67 ≥ 20% against Weiss score and Ki67 below these thresholds.

Prognostic factors for overall survival

Univariate analysis (Table 3)

At univariate analysis, the following parameters were found to be significantly inversely associated with overall survival (table 2): age $\geq$ 50 years (p=0.005), the presence of symptoms related to tumor mass (p=0.005) or hormonal hypersecretion at diagnosis (p=0.0005), ENS@T, mENS@T classification (P<0.0001), R status (R1 status (p=0.007), or R2 (p<0.0001) or Rx (p<0.001)), Weiss score >6 (p=0.03) and Ki67 $\geq$ 20% (p=0.003). Within the mENS@T classification, stage III, IVa, IVb, and IVc were found to be significantly associated with OS (p<0.001). Specifically, 2-yr OS was 72%, 42%, 22% and 12% for stages III, IVa, IVb and IVc and the 5-yr OS was 49%, 15%, 11% and 0% for stages III, IVa, IVb and IVc, respectively.

Multivariate analysis: model 1 and model 2 (Table 4)

At multivariate analysis within model 1, the following parameters were found significantly and independently associated with an increased risk of death: age $\geq$ 50 years (p<0.0001), the presence of symptoms related to tumor mass (p=0.01) or hormonal hypersecretion at diagnosis (p=0.03), the mENS@T stage (all p<0.0001).

Within model 2, the following parameters were found significant associated to an increase of risk of death: age ≥ 50 years (p<0.01), the presence of symptoms related to tumor mass (p=0.01) or hormonal hypersecretion at diagnosis (p=0.04), the mENS@T stage (all P<0.0001), the R status (p=0.0006). The HR of tumoral grade (Weiss >6 and/or Ki67 ≥ 20%) reached 1.3, with a p-value that tended to be significant (p=0.06).

In the following section the acronym GRAF for Grading, Resection status, Age, Functional symptoms is grouped together to refer to these four parameters.

Combination of prognostic parameters

We then attempted to refine the prognostic classification of ACC, combining mENS@T stage with the GRAF parameters Presence of age ≥50 yrs and/or functional symptoms was first combined with mENS@T stages within model 1 (Figure 3). Presence of unfavourable Grading or R status was subsequently combined with mENS@T stages within model 2 (Figure 4).

Figure 3 and 4 shows these GRAF parameters significantly affect the prognosis of mENSAT stage III or IVA. Five-yr OS of mENS@T stage III was 49% but ranges from 68%, when age was below 50 yrs and the tumor incidental (Figure 3A) within model 1 to 22% when tumoral grading and R status were unfavourable within model 2 (Figure 4A).

Five-years-OS of mENS@T stage IVa was 15% but ranged from 0 to 55% when age and functional symptoms were unfavourable or favourable within model 1 (Figure 3B) respectively, and ranged from 16 to 46% when tumoral grading and R status were unfavourable or favourable within model 2 (Figure 4B).

Discussion

Based on the largest cohort of patients with advanced ACC investigated so far, this collaborative study of the ENS@T network allows to refine the prognostic classification of advanced ACC patients as defined by stage III or synchronous stage IV. A new mENS@T TNM classification for advanced ACC patients is proposed as well as four additional prognostic parameters named “GRAF parameters” confirmed as critical: Grading (G), R status (R), age (A) and presence of functioning symptoms, as defined as tumor- or hormone-

related symptoms at diagnosis (F). Of note, the clinical presentation of advanced synchronous ACC in our series is in agreement with previous reports and do not suggest bias in enrolment of this retrospective series of patients (4, 6, 10, 16).

Tumor stage, as best defined by ENS@T classification, was confirmed as the keystone of the prognostic stratification of advanced ACC patients. Due to the high number of patients enrolled, we were able to further investigate the prognostic role of the N status together with venous invasion. We identify a deleterious prognostic role of the N1 status in the range of stage IV ACC patient prognosis as previously reported (9, 14) In addition, we confirm the prognostic value of the number of tumor organs including the primary but also the presence of lymph nodes (16). On the basis of these results, we herein elaborate a new prognostic TNM categorisation of advanced ACC patient, the mENS@T classification, that allows to significantly discriminate the prognostic outcomes of four categories of advanced ACC patients named stage III, IVa, IVb, IVc with 5-yrs OS of 49%, 15%, 11% and 0%, respectively. In this new classification the N1 status shifts tumours from the ENS@T stage III to the mENS@T stage IV category (i.e. stage IVa if isolated). By contrast, the prognosis of ACC patients with venous invasion was found consistent with other subgroups of the stage III N0. However, the fact that the presence of invasion to renal vein or vena cava could not be accurately documented in all cases, because it was just introduced in 2009 (6) constitutes a limitation of our study. In addition, it should be kept in mind that the N classification used in our study refers to both imaging and pathological classifications and future refinements are expected. From a therapeutic standpoint, these results may suggest that the surgery of ACC primary tumor including venous invasion is better handled by ACC surgeons than lymph node dissection whose putative role has been only be recently underlined (15, 28).

In addition to the mENS@T classification, four parameters named GRAF parameters are validated for the first time as additional complementary prognostic parameters in large series of advanced ACC patients after adjustment for tumor burden. GRAF parameters were found to significantly affect the prognosis of each mENSAT stage that should now be reported in all studies that question the role of therapeutic intervention in this rare cancer. To make this new GRAF parameters applicable for physicians in their routine practice but also due to the limited number of patients, we decided to test the prognostic influence of the GRAF parameters within most numerous mENS@T stages namely stage III or IVa . The 5-yr OS prognosis of stage III patients was found to range between 60-70% in <50 yrs-old patients with an incidentally discovered ACC or with R0 status and favourable tumoral grading but dropped to 22% when postoperatively the tumoral grading and R status were both found unfavourable. Within stage IVa patients, the 5-yrs OS prognosis was 15% but was found to range from 0 to 55% in patients with favourable or unfavourable GRAF parameters, suggesting again an overlap between stage III and IVa patients. These results strongly suggest the added value of these GRAF parameters to refine the prognostic stratification of advanced ACC patients and the need for a standardized characterization of each of them. At the end of the day, our results suggest that a 2 month difference in overall survival in phase

III trial, as recently reported in the FIRMACT trial, could be easily explained by unbalanced stratification for key prognostic parameters rather than therapeutic intervention. Age was found prognostic in some previous studies dealing with early or all stage ACC patients (4, 17, 23) but not all (16). It was expressed as a binomial parameter in this study and whether it reflects the host, presence of comorbidities, or is a marker of the tumor biology requires further investigations. The presence of symptoms whatever the subtype, tumor- or hormone-related, was also found to affect the prognosis with an identical prognostic influence. Hormonal work-up of ACC patients has been standardized for several years now and most recent series suggest a deleterious prognostic impact of cortisol secretions (17, 19). Future studies should investigate more precisely how far the magnitude and subtypes of secretions affect the prognosis (17, 19). In the same line, the general status and presence and type of tumor-related symptoms should now be more precisely defined (4, 6, 10, 16). The prognostic role of the mitotic index but also of the Ki67 even after adjustment to the stage has been suggested in previous reports (18, 27, 29). Some authors even proposed proliferative index as a more informative driver of the ACC prognostic classification than TNM stage (18, 27). We do not confirm this hypothesis in advanced ACC patients, especially as a far as a more accurate mENS@T classification is used. For reasons related to the limited number of patients with available Ki67 index, we decided to define the grading as a combination of the medians of the Weiss score and/or Ki67 index. Finally, among the GRAF parameters, grading was found to bring the weakest prognostic information. Whether the weak influence of the grade in our study is explained by a lower prognostic influence of the Weiss score in comparison with Ki67 index as suggested by univariate analysis in our study, methodological issues including absence of standardisation but also lack of pathological data in all patients, or a lower informative value of the primary tumor analysis in advanced ACC, remains to be explored. Standardization of Weiss criteria total score reading and proliferative index analysis in future pathological report is expected to represent a step forward in the evaluation of the prognostic influence of Weiss score and or proliferative index in advanced ACC patients. Although the authors consider Ki67 as more informative and despite the fact that Ki67 was found significant in a limited subgroup of advanced ACC with Ki67 available at multivariate analysis (data not shown), we suggest to use the combination of these parameters in advanced ACC patients until additional data are provided.

A lower number of studies have focused on the prognostic role of the R status and its role is debated since found prognostic in some studies (4, 9, 30) but not all (16). Indeed, R status can be considered as a surrogate of the tumor burden but also testifies of the surgeon expertise which objective analysis is difficult. R0 status was found a major prognostic parameter in our study. Interestingly, at univariate analysis, both the R0 status achieved after the resection of the primary but also the primary and metastases was significant, suggesting that the benefit of the R0 status applies not only to the primary but also to the overall tumor mass (data not shown). Obviously clinicians should ensure that life expectancy and hazards of such intervention do not jeopardize the initial medical management.

Strengths of this study include the large number of patients based on national expert European networks together with prolonged follow-up allowing robust conclusions in this rare cancer. Limitations of this study include its retrospective nature, absence of pathological reports for all patients. Standardization and further validations of the mENS@T-GRAF parameters are however needed within prospective cohort of patients as well as the analysis of the added value of the recently published molecular classification of ACC patients (31).

Conclusion

To conclude, we validate a new mENSAT classification for advanced ACC and four additional prognostic "GRAF" parameters that include the grading, R status, Age and Functional status. This new mENS@T-GRAF system allows to refine the prognosis of advanced ACC patients and is expected to impact the design of future protocols, the interpretation of retrospective studies and to help in the development of biomarkers.

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Legend of the Figures

Figure 1: Overall survival according to UICC, ENS@T and two m-ENS@T TNM classification in 444 avanced ACC patients :

(A) overall survival (OS) according to UICC stage;

(B) OS according to ENS@T;

(C) OS according to m-ENS@T (modified-stage III and modified-stage IV).

mENS@T classifications were built as follows: in the first mENS@T classification, stage III was split into two subgroups according to the N status (N0 or, N1-Nx status respectively). In the second mENS@T classification, stage III was split into two subgroups according to the venous invasion status (absence or presence of venous invasion) and compared to stage IV prognosis. In addition, stage IV was categorized into subgroups according to the number of tumor organs involved. Finally, the first mENSAT classification was found to best discriminate the outcome of advanced ACC patients

Figure 2: Overall survival of patients according Weiss score, Ki 67 or the combination in 350 advanced ACC patients:

(A) Weiss score alone ($\leq$ 6 *vs* > 6)

(B) Ki-67 ($\leq$ 20% *vs* $\geq$20%)

(C) combination of the two parameters (Ki-67 < 20 and Weiss $\leq$ 6 *vs* Ki-67 $\geq$ 20 or Weiss > 6).

Three different classifications were analysed prior the final prognostic analysis including: Weiss score as defined by global median score < 6 vs > 6, Ki67 as defined by a percentage < 20% vs > 20% or the combination of Weiss score and Ki67 (as defined by a score < 6 and Ki67 percentage < 20% or the presence of one of the two parameters). Patients whose Weiss score and Ki-67 were both missing were excluded from the analysis.

Figure 3: Kaplan Meier curves of overall survival according to age and modality of diagnosis (Model 1)

(A) mENS@T stage III

(B) mENS@T stage IVa

Prognostic factors (PF) number is calculated based on the presence or absence of age>55 yrs, and/or symptoms at diagnosis

Figure 4: Kaplan Meier curves of overall survival according to the tumoral grade (Weiss ≤ 6 and Ki<20 vs Weiss >6 and or Ki>20) and resection status (R0 vs R1,R2, Rx) (Model 2)

(A) mENS@T stage III

(B) mENS@T stage Iva

Prognostic factors (PF) number is calculated based on the presence or absence of Weiss >6 and or Ki>20 , and or R1,R2, Rx

Supplementary Figure 1:

(A) Overall survival according to the N status of stage III and the number of organs involved of stage IV ACC patients

(B) Overall survival according to the venous invasion status of stage III and the number of organs involved of stage IV ACC patients

Table 1: Stage definitions in the Union for International Cancer Control (UICC), European Network for the Study of @drenal tumor (ENS@T) and the modified ENS@T (mENS@T), as defined in Materials and methods

Staging	Definition
UICC	
III	T3N0, N1
IV	T3N1, T4, M1
ENS@T	
III	T3-4, N1
IV	T1-4, N0 or N1,M1
mENSAT	
III	T3-4, N0
IVa	T1-T4, N1 or M1 (2 organs including N)
IVb	T1-T4, N0 or N1, M1 (3 organs)
IVc	T1-T4, N0 or N1, M1 (> 3 organs)

T1: tumor ≤ 5cm; **T2:** tumor > 5 cm; **T3:** tumor infiltration in surrounding tissue histologically proven; **T4**: tumor invasion in adjacent organs or venous tumor thrombus in vena cava or renal vein. Venous tumor thrombus is only a criterion in the ENS@T classification.

N0: negative lymph nodes; **N1**: positive lymph nodes

M0: absence of distant metastases; M1 presence of distant metastases

Table 2: Main clinical and pathological characteristics of 444 advanced ACC patients

Parameters	n of patients (%)	n of evaluable patients
Patients	**444**	**444**
Age(yrs)		
<50	**200 (45%)**	**444**
≥ 50	**244 (55%)**	
Gender		
Male	**173 (39%)**	**444**
Female	**271 (61%)**	
Modality of diagnosis		
Tumoral mass	**163 (37%)**	**444**
Hormonal secretion	**144 (32%)**	
Incidenatally	**65 (15%)**	
Other or unknown	**72 (16%)**	
ENS@T stage		
III	**210 (48%)**	**444**
IV	**234 (52%)**	
modified ENS@T stage (mENS@T)		
III	**177 (40%)**	**444**
IVa	**139 (31%)**	
IVb	**75 (17%)**	
IVc	**53 (12%)**	
Tumor (T)		
T1	**11 (2%)**	**444**
T2	**97 (22%)**	
T3	**140 (32%)**	
T4	**196 (44%)**	
Regional lymph nodes (N1)		
Yes	**98 (22%)**	**300**
No	**202 (45%)**	
Unknown	**144 (32%)**	
Organ metastases (M1)		
Lung		
Yes	**152 (34%)**	**444**
No	**292 (65%)**	
Liver		
Yes	**125 (28%)**	**444**
No	**319 (72%)**	
Bone		
Yes	**32 (7%)**	**444**
No	**412 (93%)**	
R status		
R0	**152 (34%)**	**444**
R1	**34 (8%)**	
R2	**93 (21%)**	
Rx	**165 (37%)**	
Weiss score		
≤6	**174 (53%)**	**237**
>6	**153 (47%)**	
Ki 67 (%)		
<20	**103 (46%)**	**226**
≥20	**123 (55%)**	

Table 3: Significant prognostic factors on overall survival at univariate analyses

Parameters	n of patients (%)	HR (95%CI)	p value (univariate)
Age (yrs)			
<50	200	1	
≥50	244	1.4 (1.1-1.9)	0.005
Modality of diagnosis			
Incidental	65	1	
Tumoral	163	1.7 (1.2-2.6)	0.005
Hormonal hypersecretion	144	2.0 (1.4-3.0)	0.0005
ENS@T stage			
III	210	1	
IV	234	3.1 (2.4-3.9)	<0.0001
modified ENS@T stage (mENS@T)			
III	177	1	
IVa	139	2.5 (1.9-3.3)	<0.0001
IVb	75	3.9 (2.8-5.4)	<0.0001
IVc	53	5.1 (3.5-7.4)	<0.0001
R status			
R0	152	1	
R1	34	1.8 (1.2-2.9)	0.007
R2	93	3.1 (2.3-4.3)	<0.0001
Rx	165	2.1 (1.5-2.7)	<0.001
Weiss score			
≤6	174	1	
>6	153	1.3 (1.02-1.7)	0.03
Ki-67%			
<20	103	1	
>20	123	1.6 (1.2-2.3)	0.003

Table 4: Multivariate analyses (model 1 and 2)

	Model 1 (N=444 pts)			Model 2 (N=349pts)		
	Hazard ratio	**95% CI**	**p**	**Hazard ratio**	**95% CI**	
Age						
<50 yrs	1	1		1	1	
≥ 50 yrs	1.6	1.3-2.1	p<0.0001	1.4	1.1-1.8	
Diagnosis modality						
Incidentally	1	1		1	1	
Tumoral	1.6	1.1-2.5	0.01	1.7	1.1-2.7	
Hormonal hypersecretion	1.6	1.03-2.3	0.03	1.6	1.01-2.5	
Other or unknown	1.2	0.8-1.9	0.42	1.1	0.7-1.8	
Modified ENS@T stage						
III	1	1		1	1	
IVa	2.6	2.0-3.5	p<0.0001	2.1	1.5-2.9	
IVb	3.8	2.7-5.3	p<0.0001	2.7	1.8-4.0	
IVc	4.9	3.4-7.2	p<0.0001	3.7	2.4-5.8	
Tumoral grade						
Weiss ≤ 6 and Ki<20	NA			1	1	
Weiss >6 and or Ki≥20				1.3	0.98-1.7	
R status						
R0	NA			1	1	
R 1 2 x				1.7	1.3-2.3	

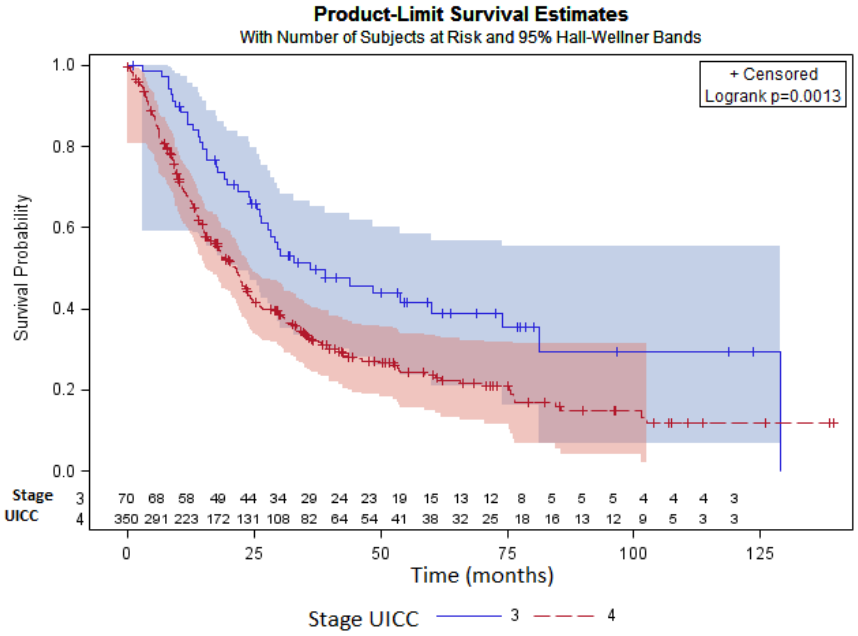
Model 1: prognostic model with clinical variables, without pathology and R status,

Model 2: prognostic model with clinical variables, with pathology and R status,

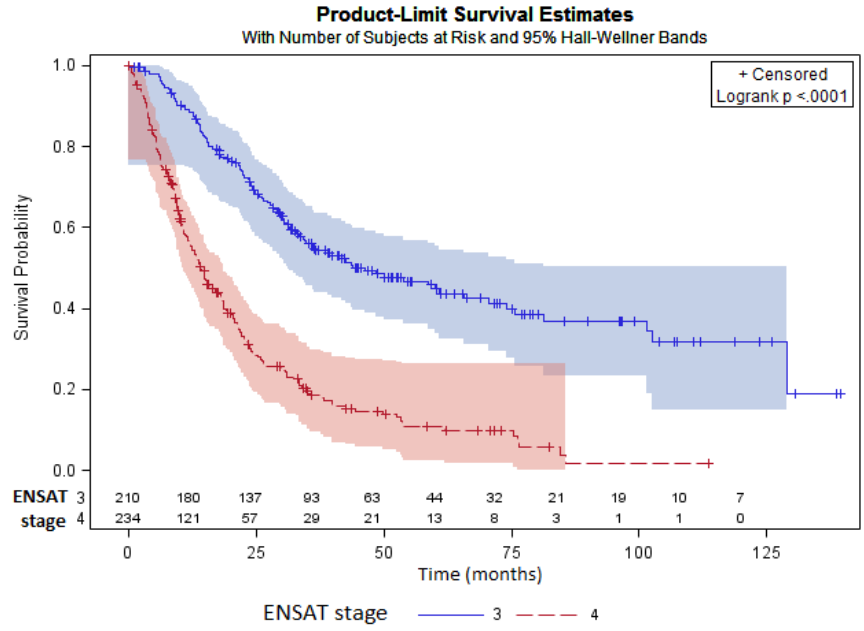
NA= not applicable

Figure 1:

A: UICC stage



B: ENS@T stage



C: modified ENS@T (mENS@T)

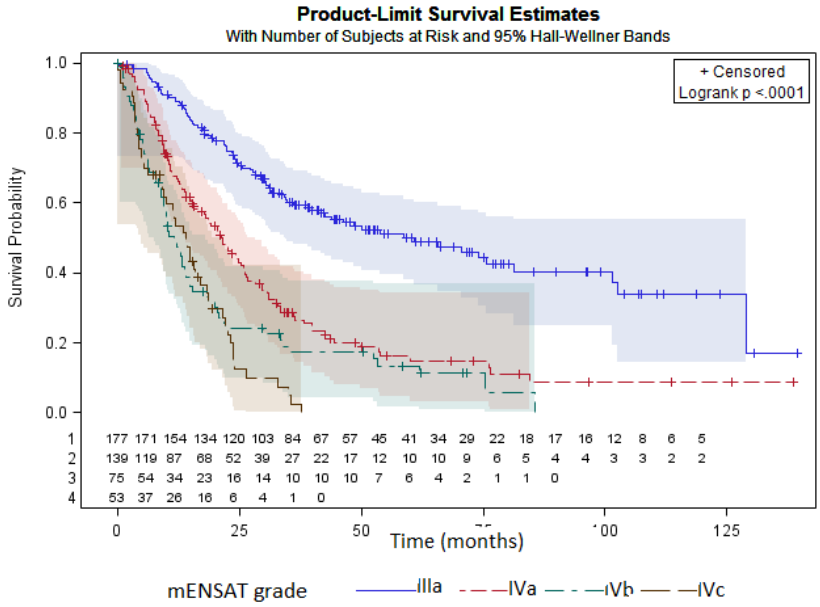
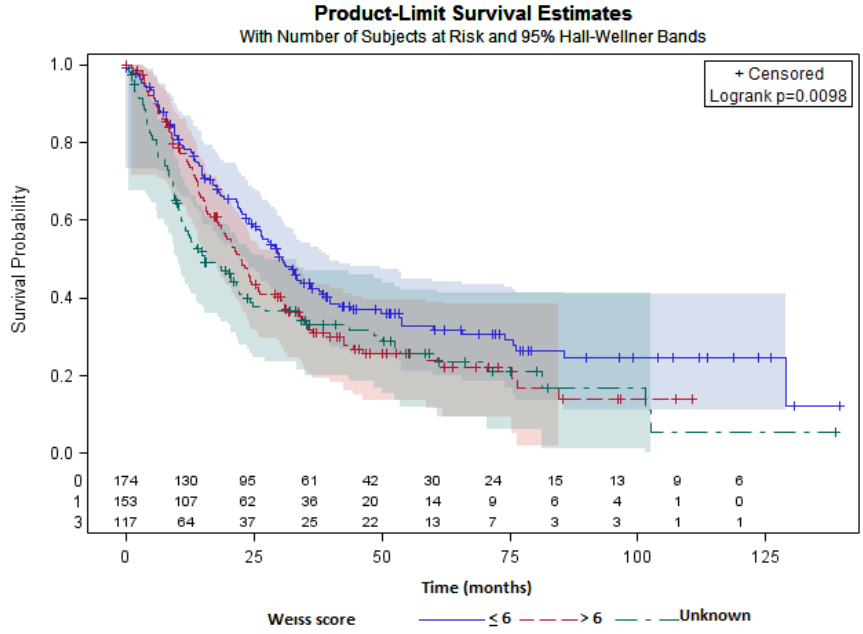
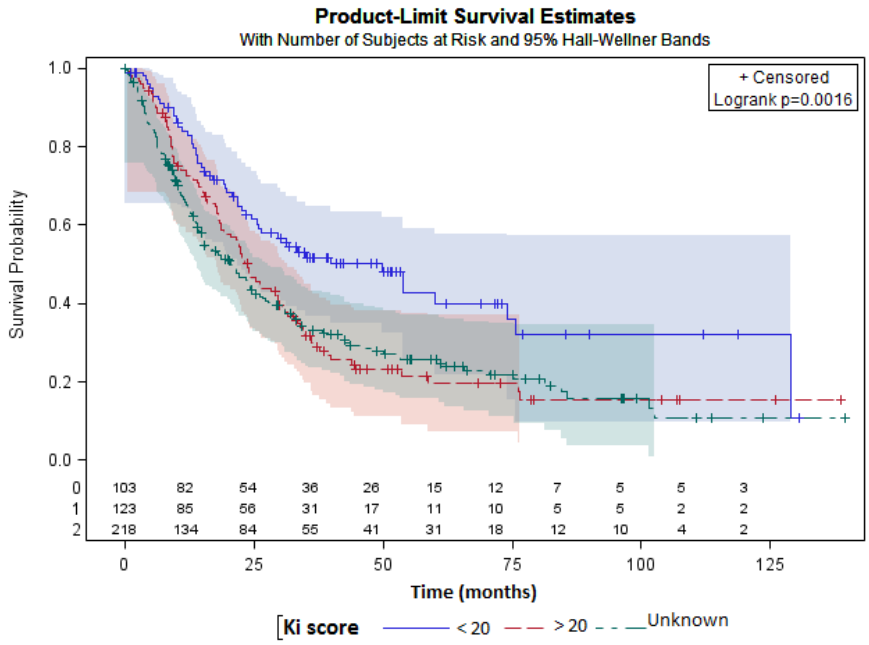


Figure 2:

A: According to the Weiss score only



B: According the Ki67 score only



C: OS according the combination of Weiss score and Ki67index

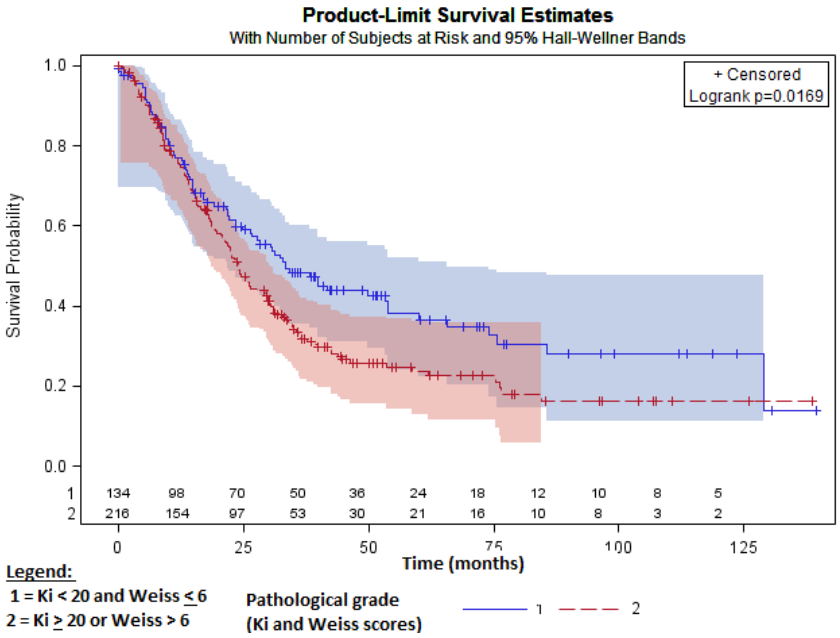
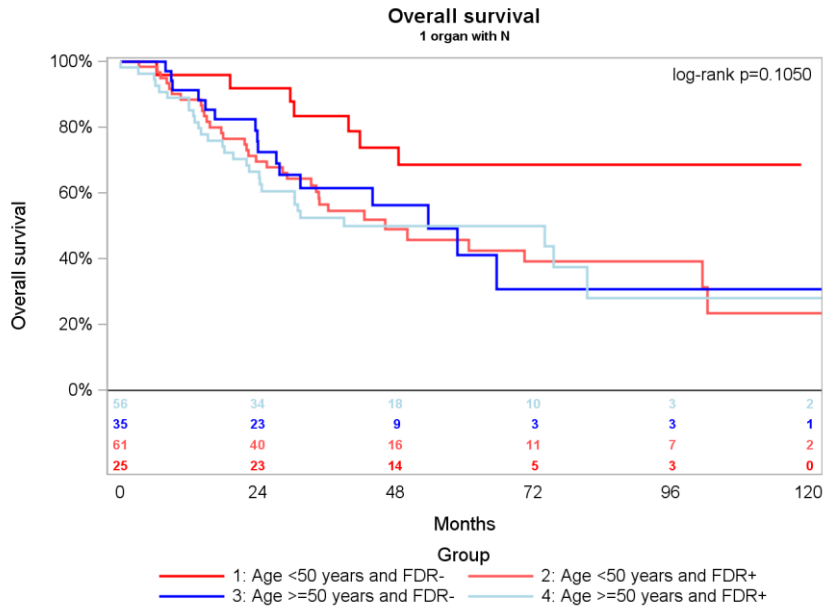


Figure 3:

A: mENS@T stage III ATTENTION LA LEGENDE NO COLLE PAS/ ENLEVER FDR ET METTRE SYMPTOM PRESENCE-ABSENCE



B: mENS@T stage IVa ATTENTION LA LEGENDE NO COLLE PAS/ ENLEVER FDR ET METTRE SYMPTOM PRESENCE-ABSENCE

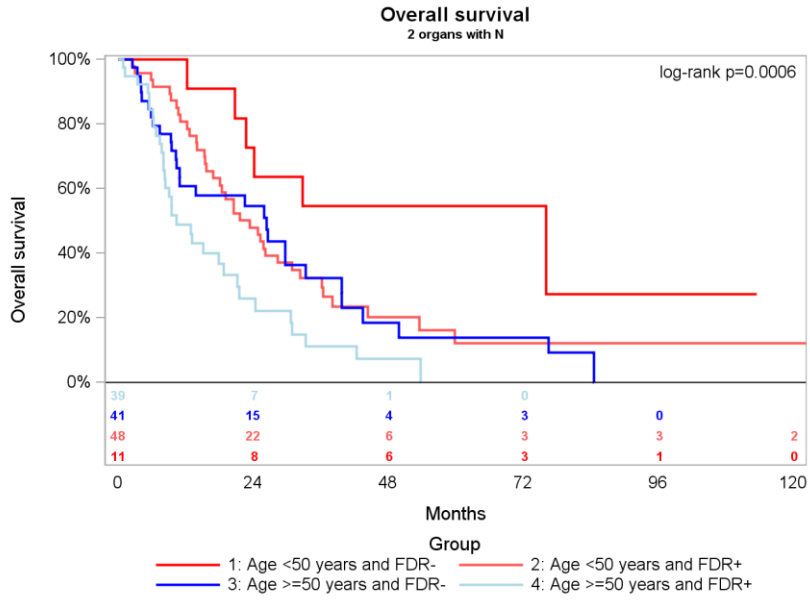
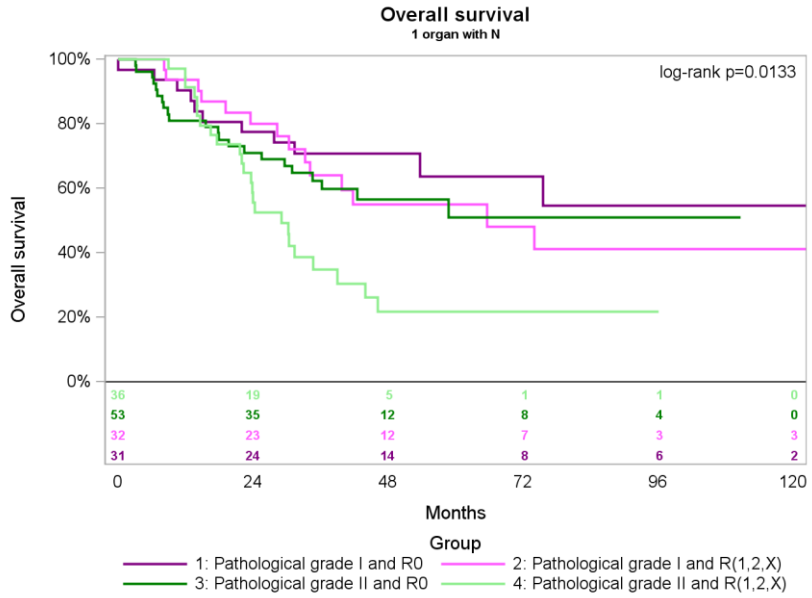
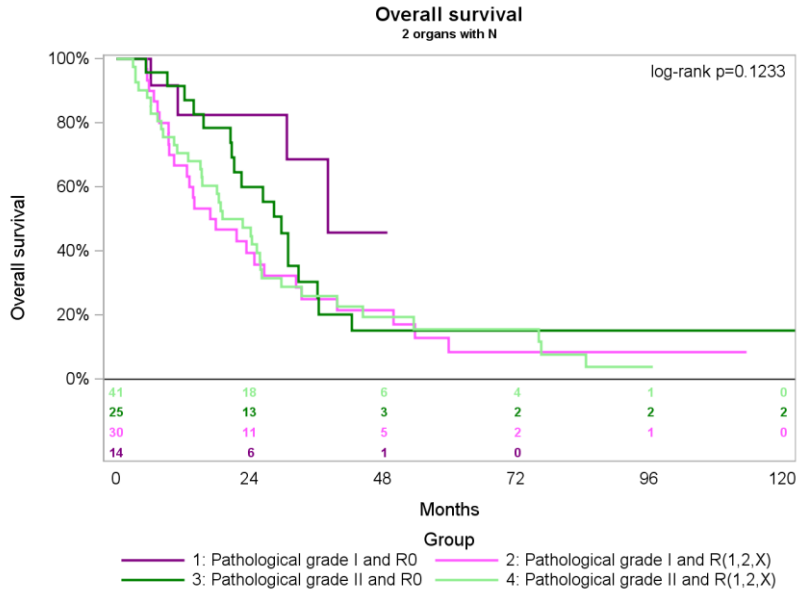


Figure 4

A: mENS@T stage III



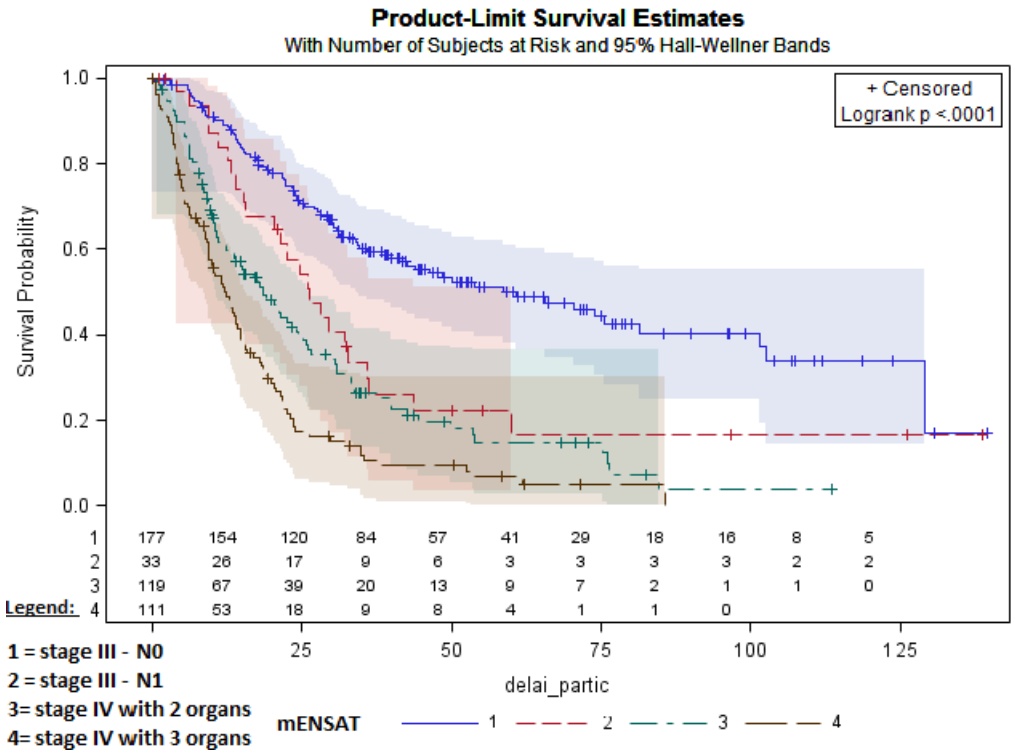
B: mENS@T stage IVa



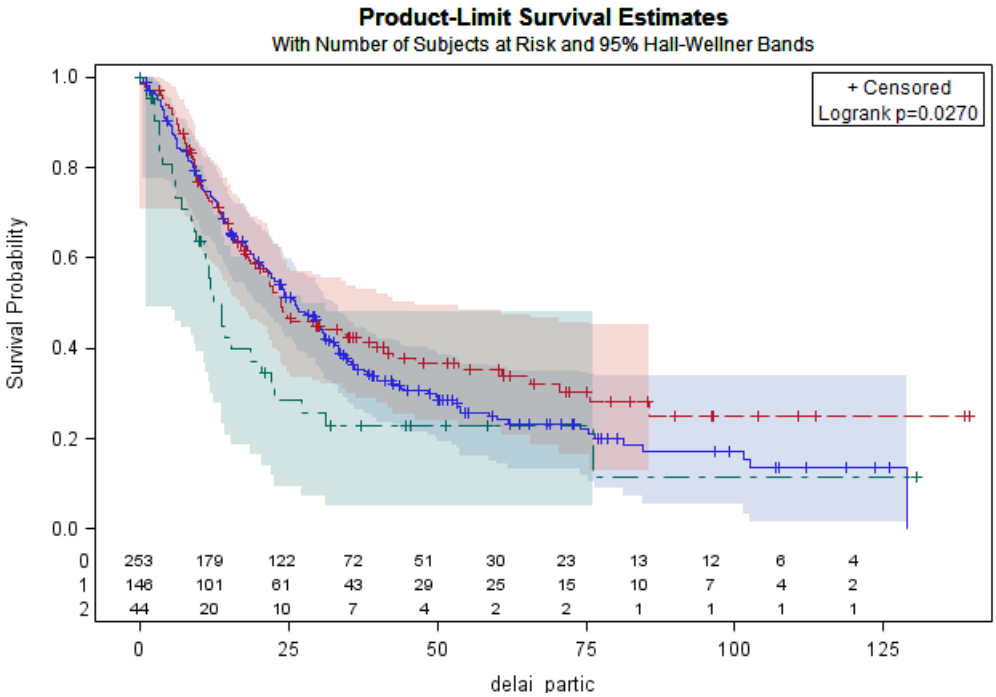
Appendix

Supplementary figure 1:

A



B


Product-Limit Survival Estimates
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Logrank p=0.0270
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0 253 179 122 72 51 30 23 13 12 6 4
1 146 101 61 43 29 25 15 10 7 4 2
2 44 20 10 7 4 2 2 1 1 1 1
0
25
50
75
100
125
delai partic

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